A PILOT STUDY OF THE IMPACT OF A RAPID ART INITIATION IN ADVANCED HIV DISEASE (Rainbow study)

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Background

• HIV presentation with advanced disease is an unfavourable prognostic condition, characterized by high morbidity and mortality [1,2].
• Rapid ART initiation has been associated with greater retention in care, better virological control and better overall outcomes than standard initiation in low–middle income countries [3,4].
• Evidence of the benefits of rapid ART initiation in high-income countries are growing (e.g. REACH program, Rapid ART program [US], Diamond trial, STAT trial).
• Rapid ART initiation in people with advanced HIV disease could improve the outcomes, but data on this strategy are lacking.

AIM: To evaluate the feasibility, efficacy and safety of rapid antiretroviral initiation strategy (within 7 days from HIV diagnosis) based on bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in HIV-infected naïve individuals presenting with an Advanced HIV disease.

Methods

Study design: Pilot, monocentric, single-arm, prospective, phase IV, sponsored clinical trial.

Population: 30 ART-naïve participants presenting at HIV-1 diagnosis with advanced disease described as the presence of an AIDS-defining event and/or CD4 cells count <200 µL.
Exclusion criteria: a) CrCl < 30 mL/min; b) severe hepatic impairment; c) active tuberculosis; d) cryptococcosis; e) pregnant/breastfeeding women; f) systemic cancer chemotherapy; g) age < 18 years

Endpoints: To evaluate time-to-clinical or virologic failure (VF) defined as failure to achieve:
a) HIV-RNA reduction > 1 log $_{10}$ copies/ml by W12; b) HIV-1 RNA ≤200 copies/mL at or after 24 weeks;
c) HIV-1 RNA ≤ 50 copies /ml at any time after W48.
Safety, feasibility, neurocognitive performance and PROs were assessed as well.

Procedures:
- B/F/TAF 50/200/25 mg was started within 7 days of HIV diagnosis.
- Viral and immunologic parameters were evaluated at BL, w4, w12, w 24, w36, w48.
- eGFR by MDRD and BMI were evaluated at BL and w48.
- Neurocognitive assessment, measured by the mean of 12 test examining 5 domains: speed of mental processing; mental flexibility; memory; fine motor functioning; short-term memory/ working memory, were performed at BL and w48.
- Patient Reported Outcomes (PROs), that evaluated health-related quality of life trough: 1) Beck Anxiety Inventory (BAI); 2) Beck Depression Inventory (BDI); 3) Pittsburgh Sleep Quality Index (PSQI); 3) Short Form Health Survey (SF-12); 4) Health questionnaire (EQ-5D), were performed at BL and w 48.

Statistical analysis:
To analyse repeated measurements, the Kenward-Roger method was used.

Results 1

Feasibility:
Among 116 new HIV diagnosis from May 2020-January 2021, 40 (34%) had advanced HIV disease. 30 fulfilled eligibility criteria and were enrolled **(Figure 1).**

Efficacy:
- Virologic failures: 1 participant had HIV-RNA 59 copies/mL at W48 and was undetectable 3 months later; 1 participant had HIV-RNA 233 copies/mL at W48 and was undetectable 4 months later.
Clinical failure: 1 participant was diagnosed with disseminated TB 9 days after the BL visit, and ART was switched.
No ART modification was performed once GRT was reviewed: no NRTI mutations, 3 accessory INSTI mutations (E157Q, G163K, L74I).
- Viro-immunological parameters improved during study period **(Figure 2).**

Safety:
No ART discontinuation due to toxicity or virologic failure was observed.
3 pts had 6 SAEs (3 unrelated; 3 potentially related to B/F/TAF):
Pt 1: seizure (w4 and w12) + PML with IRIS (w5);
Pt 2: *Pneumocystis* pneumonia with IRIS (w4) + pneumomediastinum (w5);
Pt 3: clinical worsening (w1) + acute appendicitis and disseminated TB with IRIS (w2) that required ART switch.
- Metabolic and renal parameters are shown in **Figure 3.**

	(N=30)
Female sex*	5 (16.7%)
Age**	45 (38-58)
Risk factor **	
MSM	5 (16.7%)
Heterosexual	10 (33%)
Other/unknown	15 (50%)
Caucasian ethnicity*	27 (90%)
CDC stage*	
A	13 (43.3%)
B	4 (13.3%)
C§	13 (43.3%)
CD4 cell count at BL, cell/mmc**	90 (39-147)
CD4/CD8* at BL	0.14 (0.09-0.24)
HIV RNA at BL, log$_{10}$ cp /ml**	6.0 (5.4-6.4)
≥ 1 comorbidity*	12 (40%)
HCV coinfection*	1 (3%)
HBV coinfection*	0
Days from HIV diagnosis to BL**	6 (5-7)

Table 1. BL demographic and clinical characteristics.
*n (%); ** median (interquartile range)
§ Of the CDC stage C: 7 *Pneumocystis* pneumonia, 5 Kaposi's sarcoma, 1 HIV-associated encephalopathy

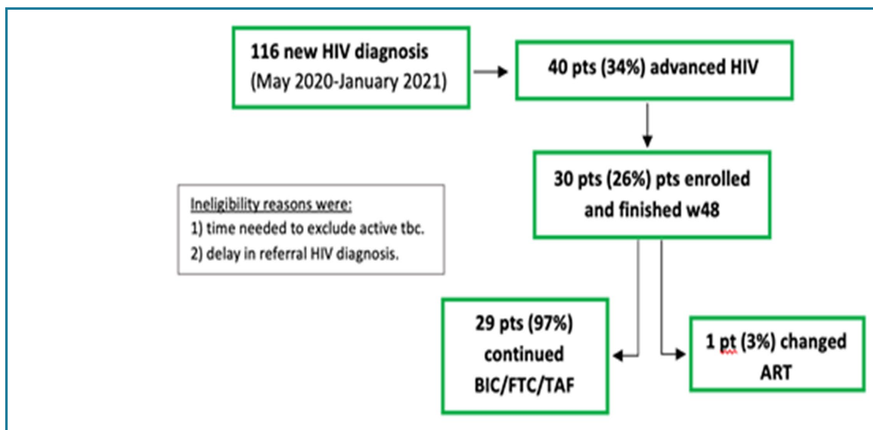

Figure 1.Feasibility.

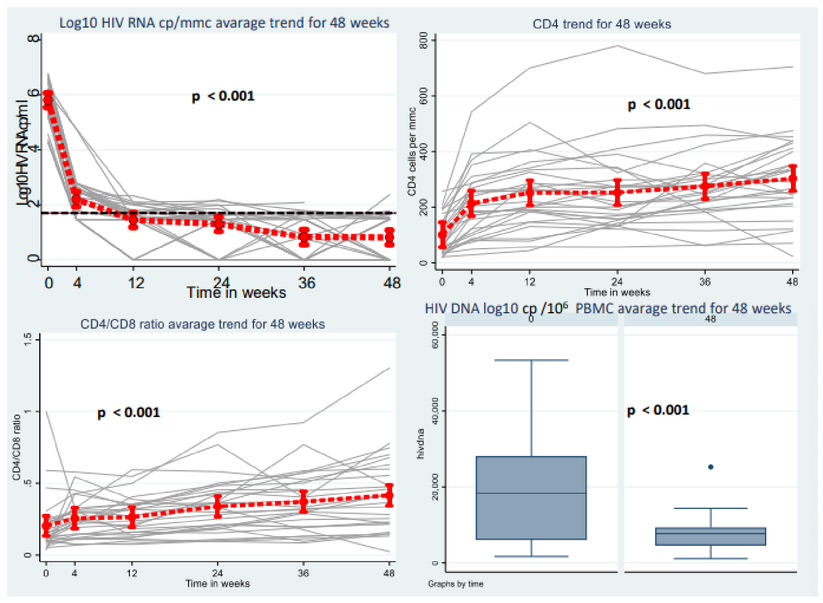

Figure 2. HIV-RNA and HIV-DNA decreased while CD4 count and CD4/CD8 improved and during study period.

Figure 3. The estimated glomerular filtration rate, by MDRD, decreased slightly. BMI increased from 22.7 to 24.8.

Results 2

Neurocognitive outcomes:
- 12/25 participants (44%) and 4/22 participants (18%) presented HAND respectively at BL and w48, according to Frascati criteria [5].
- The total cognitive performance significantly improved during study period, mostly due to the improvement of verbal learning and memory, executive functions and working memory domains.
- At w48 all the cognitive domains resulted within 1 standard deviation below normative values, except for the processing speed **(Table 2).**
- BDI, BAI and PSQI did not change during study period **(Table 3).**
- The subjective perception of physical and mental health status measured by EQ-5D improved, while physical and mental health status measured by 12 Item Short Form survey (SF-12) did not show significant changes over time **(Figure 4).**

Table 2. Neurocognitive performance during study period.

Score	time	N	Z-Score over time					Z-score vs reference value	
			mean	diff	95% CI		P-value	1SD-P	2SD-P
Processing speed	0	27	-1.70					**0.000**	0.954
	48	22	-1.57	0.13	-0.21	0.46	0.459	**0.000**	1.000
Mental flexibility	0	25	-0.33					1.000	1.000
	48	20	-0.02	0.32	-0.03	0.66	0.070	1.000	1.000
Memory	0	27	**-0.86**					0.704	1.000
	48	22	**-0.41**	0.46	0.15	0.76	**0.003**	0.966	1.000
Fine motor functioning	0	27	**-0.87**					0.641	0.998
	48	22	**0.29**	1.16	0.58	1.73	**0.000**	1.000	1.000
Working memory	0	27	**-0.87**					0.784	1.000
	48	22	**-0.63**	0.24	0.00	0.48	**0.049**	0.985	1.000
NPZ 12	0	25	**-0.79**					0.971	1.000
	48	20	**-0.46**	0.33	0.15	0.52	**0.001**	1.000	1.000

Table 3. BDI, BAI, PSQI during study period.

Score		Time 0	Time 48	P-value
BDI	<20	25	21	1.000
	≥20	2	1	
Somatic-affective BDI	<20	27	22	na
	≥20	0	0	
Cognitive BDI	<20	3	4	0.685
	≥20	24	18	
BAI	< 16	23	20	0.678
	≥16	4	2	
PSQI	<=5	20	19	0.706
	>5	5	3	

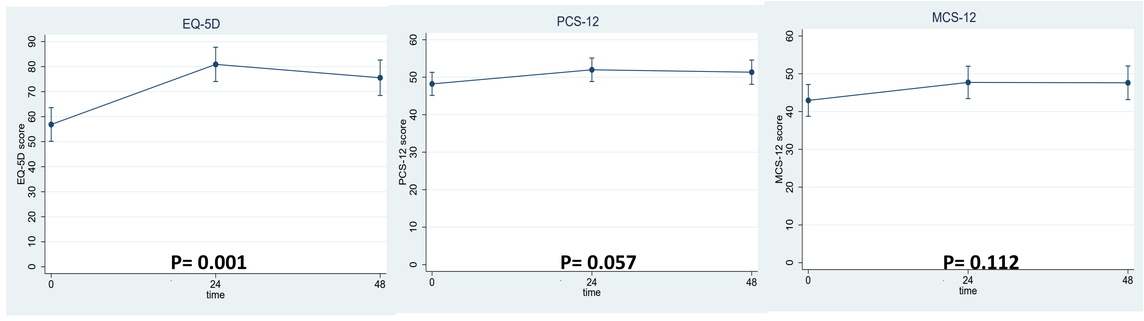

Figure 4. EQ-5D average improved from 57/100 to 75/100. physical. The average of Physical Component Score (PCS) of SF-12 changed from 48 to 51, while the average of Mental Component Score (MCS) of SF-12 passed from 43 to 48.

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Conclusions

Rainbow results support the feasibility, efficacy and safety of a rapid start strategy using B/F/TAF in people with advanced HIV disease.

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